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bothersome symptom (MBS) of moderate-to severe dyspareunia; and anticipated sexual activity (with vaginal penetration) during the trial period. Vulvar and vaginal atrophy (VVA) treatments, including vaginal lubricants and moisturizers, were discontinued within 7 days prior to screening. Use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products were prohibited within 8 weeks of study start. Changes from baseline in total and individual domain FSFI scores for each dose were compared with placebo using ANCOVA with baseline as a covariate.

764 postmenopausal women were randomized to 4 µg (n=191), 10 µg (n=191), or 25 µg (n=190) vaginal estradiol softgel capsules or placebo (n=192). The majority of the women were white (87%) with a mean age of 59 years and a mean BMI of 26.7 kg/m<sup>2</sup> (Table 145). The FSFI questionnaire was completed by those who were not in the PK sub-study (n=692; 90.6%). The average baseline total FSFI score of 14.8 for all women indicated FSD in the subjects.

TABLE 145

| Summary of subjects enrolled in study |                                    |                                     |                                     |                            |
|---------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|----------------------------|
|                                       | Composition 4<br>4 µg<br>(n = 186) | Composition 5<br>10 µg<br>(n = 188) | Composition 6<br>25 µg<br>(n = 186) | Composition 7<br>(n = 187) |
| Age, years                            |                                    |                                     |                                     |                            |
| Mean ± SD                             | 59.8 ± 6.0                         | 58.6 ± 6.3                          | 58.8 ± 6.2                          | 59.4 ± 6.0                 |
| Race, n (%)                           |                                    |                                     |                                     |                            |
| White                                 | 162 (87.1)                         | 165 (87.8)                          | 161 (86.6)                          | 160 (85.6)                 |
| Black or African American             | 20 (10.8)                          | 21 (11.2)                           | 24 (12.9)                           | 21 (11.2)                  |
| Asian                                 | 3 (1.6)                            | 2 (1.1)                             | 1 (0.5)                             | 1 (0.5)                    |
| BMI, kg/m <sup>2</sup>                |                                    |                                     |                                     |                            |
| Mean ± SD                             | 26.6 ± 4.9                         | 26.8 ± 4.7                          | 26.9 ± 4.8                          | 26.6 ± 4.6                 |
| Baseline total FSFI Score             |                                    |                                     |                                     |                            |
| Mean ± SD                             | 14.8 ± 6.13                        | 15.8 ± 6.24                         | 14.2 ± 6.21                         | 14.4 ± 6.61                |
| Baseline FSFI Pain Score              |                                    |                                     |                                     |                            |
| Mean ± SD                             | 1.6 ± 1.11                         | 1.8 ± 1.22                          | 1.7 ± 1.17                          | 1.7 ± 1.20                 |

The Female Sexual Function Index (FSFI) total summary score is a numerically continuous measure that was descrip-

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tively summarized at Visits 2 and 6 and the change in the total summary score (Visit 6 minus Visit 2) was also descriptively summarized. The domain sub-scores and the changes in the domain sub-scores were also descriptively summarized. Summaries were by treatment arm, and all active treatment arms combined.

In addition, the change in mean from baseline of each active treatment group from the placebo group for each numerically continuous endpoint was evaluated. The least square (LS) mean changes and the 95% CI for the difference in LS Mean changes between treated and placebo are provided. The FSFI Questionnaire consists of 19 questions divided among 6 domains, and has a minimum total score of 2.0 and a maximum score of 36.0 points. The FSFI questionnaire was administered to the randomized population except for those subjects in the PK sub-study. At Baseline, the overall mean Total Score was 14.8 (14.8 for the 4 µg group; 15.8 for the 10 µg group; 14.2 for the 25 µg group; and 14.4 for the placebo group). The LS mean change in the FSFI Total Score and domain scores from Baseline to Week 12 are summarized in Table 146.

Change from Baseline to Week 12 in FSFI total score and domains compared to placebo was assessed.

After 12 weeks, total FSFI scores numerically improved from baseline in all groups, including placebo. Total FSFI score significantly increased with the 10 µg group (P<0.05) and the 25 µg group (P=0.0019) versus placebo (FIG. 24).

FSFI lubrication and pain domain scores improved numerically in all groups including placebo from baseline to 12 weeks; improvements for the 10 µg group and the 25 µg group were statistically significantly greater than with placebo (FIG. 25A). The 25 µg composition significantly improved FSFI arousal (P=0.0085) and satisfaction (P=0.0073) domain scores at 12 weeks (FIG. 25B, FIG. 25C). All three doses were comparable to placebo in their effect on the FSFI domains of desire and orgasm (FIG. 25D, FIG. 25E). The 4 µg composition and placebo provided similar levels of improvement. The compositions improved FSFI in a dose-dependent manner, with the 25 µg dose having the greatest improvement. All three doses were efficacious, and the numeric improvement in subjective symptoms was highest for subjects in the 10 and 25 µg groups. The observed placebo response could be attributed to the coconut oil (Miglyol) in the formulation for the placebo and the estradiol compositions, which may also contribute to the observed benefits.

TABLE 146

| Female Sexual Function Index Total and Domain Scores: |          |       |        |       |        |        |        |         |       |
|---|----------|-------|--------|-------|--------|--------|--------|---------|-------|
| Category  | Score    | 4 µg  |        | 10 µg |        | 25 µg  |        | Placebo |       |
|   |          | Mean  | SD     | Mean  | SD     | Mean   | SD     | Mean    | SD    |
| Total   | Baseline | 14.8  | 6.13   | 15.8  | 6.24   | 14.2   | 6.21   | 14.4    | 6.61  |
|   | Week 12  | 22.6  | 8.4    | 24.8  | 7.59   | 24.8   | 7.59   | 22      | 8.54  |
|   | Change   | 7.98  | 7.551  | 8.85  | 7.361  | 10.49  | 8.176  | 7.74    | 8.41  |
|   | LS Mean  | 7.909 | 0.9075 | 9.431 | 0.0492 | 10.283 | 0.0019 | 7.458   | —     |
| Arousal   | Baseline | 2.8   | 1.44   | 2.9   | 1.43   | 2.7    | 1.5    | 2.7     | 1.41  |
|   | Week 12  | 3.6   | 1.61   | 4.1   | 1.47   | 4.1    | 1.39   | 3.6     | 1.52  |
|   | Change   | 0.88  | 1.615  | 1.16  | 1.632  | 1.43   | 1.646  | 1.02    | 1.607 |
|   | LS Mean  | 0.876 | 0.9777 | 1.288 | 0.0581 | 1.393  | 0.008  | 0.927   | —     |
| Desire  | Baseline | 2.6   | 1.01   | 2.7   | 1.13   | 2.6    | 1.09   | 2.7     | 1.07  |
|   | Week 12  | 3.3   | 1.11   | 3.5   | 1.13   | 3.5    | 1.06   | 3.3     | 1.21  |
|   | Change   | 0.64  | 1.065  | 0.78  | 1.113  | 0.87   | 1.105  | 0.62    | 1.102 |
|   | LS Mean  | 0.626 | 1      | 0.801 | 0.2753 | 0.849  | 0.1139 | 0.628   | —     |